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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/722,374	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,15-18,21 and 24-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-11,21 and 25* is/are allowed.

6)☒ Claim(s) *12,15-18,24 and 26* is/are rejected.

7)☒ Claim(s) *27-31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included cancellation of claims 13, 14, 19, 20, 22 and 23, addition of new claims 27-31 and amendment to claims 1, 2, 3, 5, 7, 15-18, 21 and 24-26, filed on 2/13/2006, is made of record. Claims 1-12, 15-18, 21 and 24-31 are now pending.

In view of applicants' response, the 112 second paragraph rejection of claims 1-26 and 112 first paragraph rejection of claims 1-26 as applied to prodrug and derivative have been obviated. However, the following apply.

Claim Objections

Claims 27-31 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend on another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims are not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18, 24 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating diabetes and Alzheimer's disease does not reasonably provide enablement for treatment any or all diseases including those yet to be linked with the various mode of action embraced in the claim language. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of inhibiting or treating a disease in a patient of based on the mode of action as Aurora-2, GSK-3 and phosphoryrlation of protein (Tau or β-catenin which as recited reads on any or all diseases of these organs for which there is no enabling disclosure. These claims are deemed as reach through claims wherein based on the mode of action, treating any or all diseases is embraced. The scope of the claims includes treatment of any or all of diseases, which are not adequately enabled solely based on the activity of the compounds, provided in the specification at pages 69-70. The instant compounds are disclosed have Aurora-2, GSK-3 inhibitory activity & inhibition of phosphorylation of protein. It is therefore recited that the instant compounds are useful in treating any or all diseases for which applicants provide no competent evidence. Reading specification it appears that instant compound is useful for treating all sorts of diseases for which applicants have not provided any experimental support or nexus. Prior art search and those cited in the Information disclosure statement do not lend support to, except for treating diabetes, treatments of all diseases embraced in the claim language. That a single class of compounds can treat all or any disease of the said organs is an incredible finding for which applicants have not provided enabling disclosure and the Information Disclosure Statement suggest the use of these inhibitors is still under experimental stage and speculative in nature. Prior art search also shows that further studies are needed. See Kim et al. Differentiation and Gene Regulation 508-514, 2000 and Warner et al.,

Molecular Cancer Therapeutics 2: 589-595, 2003. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as Alzheimer's disease, multiple sclerosis, ALS etc. are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition". The scope of the claims involves all of the thousands of compounds of claim 1 as well as the thousand of diseases embraced by the terms Aurora-2 mediated disease and or GSK-3mediated disease.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of pathology of disease and their treatment.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the

requirement for undue experimentation. See Kim et al. Differentiation and Gene Regulation 508-514, 2000 and Warner et al., Molecular Cancer Therapeutics 2: 589-595, 2003.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating several diseases of that require Aurora-2 a and GSK-3 inhibitory activity as well as inhibition of phosphoryrlation of protein

2) The state of the prior art: A recent publication in the Information Disclosure Statement as well as in the specification suggest that Aurora-2, and GSK-3 are still in experimental stage. See Kim et al. Differentiation and Gene Regulation 508-514, 2000 and Warner et al., Molecular Cancer Therapeutics 2: 589-595, 2003.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the therapeutic effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the

degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show therapeutic effect and the state of the art is that the effects of Aurora-2, GSK-3 inhibitors and phosphorylation of Tau protein inhibitors are still in experimental stage

6) The breadth of the claims: The instant claims embrace treatment of several diseases including those yet to be related to Aurora-2 and GSK-3 activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make

and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action except that claim 25 is now excluded from this rejection.

Applicants' traversal to overcome this rejection is not persuasive.

First of all, applicants' assertion that the examiner had not met the burden of establishing prima facie case of nonenablement, is totally incorrect and lacks factual support.

One trained in the art would clearly see from the above rejection that examiner had considered Wands factor and had made the above rejection on the basis that based on the mode of action of the instant compounds the scope of treating any or all diseases is not enabled. Examiner had supported his position with prior art non-patent literature.

Hence, it is applicants' burden to show that based on the mode of action of the instant compound and the method of use for treating diabetes, any or all diseases can be treated. Applicants have failed to provide any such factual support.

Secondly, applicants had argued that there are several drugs for treating Alzheimer's disease but this does not mean instant claims are enabled for treating any or all diseases. In fact, the currently available drugs for Alzheimer's disease are not kinase inhibitors.

In addition, Aricept, Gleevec and Taxol on which applicants rely for factual support are yet to be known for treating any or all cancers.

For want of any factual support for objective enablement based on the mode of action for treating any or all cancer and other diseases generically embraced in the instant claims 15-18, 24 and 26, this rejection is deemed as proper and is maintained.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting Aurora-2 and GSK-3 activity in a standard biological assay recited in page 69-70, does not reasonably provide enablement for a method of inhibiting Aurora-2 or GSK-3 activity in a biological sample in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 12 is drawn to 'a method of inhibiting Aurora-2 or GSK-3 activity in a biological sample' and the term "biological sample" is not defined in the specification (see page 18, paragraph 1, page 42, paragraph 2, page 64, paragraph 1) Hence, the term biological sample would include, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof".

First, the instant claim 12 is a 'reach through' claim. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through to the corresponding therapeutic method of any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

As can be seen from the definition of the term "biological sample", without limitation it reads on many and all types of biological samples, which can include mammals or animals and therefore, the claimed method is seen to encompass an inhibitory method wherein the compound is administered to an animal. This is further evident from the purpose of the inhibition of Aurora-2 or GSK-3 activity stated in specification at various places for treating various diseases. As the inhibition of Aurora-2 or GSK-3 activity in a biological sample is disclosed to be useful, it implicitly reads on the inherent therapeutic methods characterized by the activity, which as per the specification includes numerous types of diseases/disorders recited in specification.

The sole testing assay provided in the specification at page 69-70 is to test the ability of the compounds to inhibit Aurora-2 or GSK-3β activity using a standard coupled enzyme system, however, there is insufficient guidance in the disclosure regarding the provided assay. First, the specification provides that the coupled enzyme system is provided in Fox et al., however, the cited article deals with inhibition of p38 MAP kinase activity. Next, applicant has not provided how this correlates with the efficacy in all types of biological samples encompassed by the instant method and their use in the various purposes wherein the inhibition activity is useful. For example, blood transfusion is the process of transferring blood or blood-based products from one person into the circulatory system of another. Blood transfusions may be seen as a procedure to treat some medical conditions, such as massive blood loss due to trauma, surgery, shock and where the red cell producing mechanism (or some other normal and essential component) fails. Similarly, an organ transplantation is the transplantation of a whole or partial organ from one body to another (or from a donor site on the patient's own body), for the purpose of replacing the recipient's damaged or failing organ with a working one from the donor site. As can be seen from the above, without limitation these purposes are intended for therapeutic methods and applicant has not provided competent evidence sufficient to enable the claimed method.

Therefore, the instant claim appears to be directed to the various types of therapeutic methods associated with Aurora-2 or GSK-3 inhibition activity.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of

the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Allowable Subject Matter

Claims 1-11, 21 and 25 are allowed.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any

inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

4/29/2006